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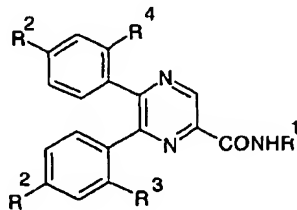
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(54) Title: PYRAZINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)

(57) Abstract: The present invention relates to compound of formula (I) and pharmaceutically acceptable salts, solvates and crystalline forms thereof, in which R<sub>1</sub>? represents cyclohexyl, 1-piperidinyl or phenyl; R<sub>2</sub>? represents H, chloro, bromo, methyl or methoxy; and when R<sub>3</sub>? represents H, R<sub>4</sub>? represents H or chloro; and when R<sub>3</sub>? represents chloro, R<sub>4</sub>? represents H or chloro; to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders particularly obesity, to methods for their therapeutic use and to pharmaceutical compositions containing them.

## PYRAZINE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

### Field of invention

- 5 The present invention relates to certain pyrazine carboxamide compounds of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

### 10 Background of the invention

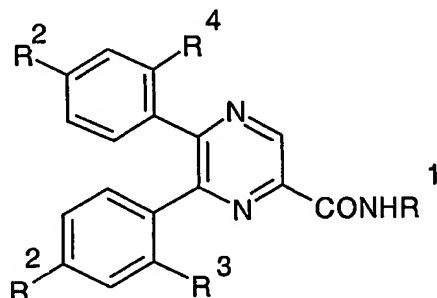
- It is known that certain CB<sub>1</sub> modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354). However, there is a need for CB<sub>1</sub> modulators with improved  
15 physicochemical properties and/or DMPK properties and/or pharmacodynamic properties.

Pyrazinecarboxamides are reported to possess antithrombotic properties (WO 92/ 02513). 5,6-Diphenyl-2-pyrazinecarboxylic acid is disclosed in CH 458 361.

20

### Description of the invention

The invention relates to compounds of the general formula (I)



- 25 and pharmaceutically acceptable salts, solvates and crystalline forms thereof, in which R<sup>1</sup> represents cyclohexyl, 1-piperidinyl or phenyl;

$R^2$  represents H, chloro, bromo, methyl or methoxy; and  
when  $R^3$  represents H,  $R^4$  represents H or chloro; and  
when  $R^3$  represents chloro,  $R^4$  represents H or chloro.

5 Further values of  $R^1$  in compounds of formula I now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one group of compounds of formula I,  $R^1$  represents cyclohexyl.

In a second group of compounds of formula I,  $R^1$  represents 1-piperidinyl.

10 In a third group of compounds of formula I,  $R^1$  represents phenyl.

"Pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a  
15 compound of Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium, calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as  
20 methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in  
25 different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The  
30 diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be

made by chiral synthesis from chiral starting materials under conditions that will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

5 Specific compounds of the invention are:

- N*-(1-piperidinyl)- 5,6-diphenyl-2-pyrazinecarboxamide;  
*N*-(1-piperidinyl)- 5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide;  
*N*-(1-piperidinyl)- 5,6-bis(4-methylphenyl)- 2-pyrazinecarboxamide;  
10 *N*-(1-piperidinyl)- 5,6-bis(4-methoxyphenyl)- 2-pyrazinecarboxamide;  
*N*-(1-piperidinyl)- 5,6-bis(4-chlorophenyl)- 2-pyrazinecarboxamide;  
*N*-(1-piperidinyl)- 5,6-bis(2-chlorophenyl)- 2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-diphenyl-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide;  
15 *N*-cyclohexyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-chlorophenyl)- 2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide;  
*N*,5,6-triphenyl-2-pyrazinecarboxamide;  
20 *N*-phenyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide;  
*N*-phenyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide;  
*N*-phenyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide;  
*N*-phenyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide;  
*N*-(1-piperidinyl)- 5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)-2-pyrazinecarboxamide; and  
25 *N*-(1-piperidinyl)- 6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-pyrazinecarboxamide;  
and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as well as pharmaceutically acceptable salts, solvates and crystalline forms thereof.

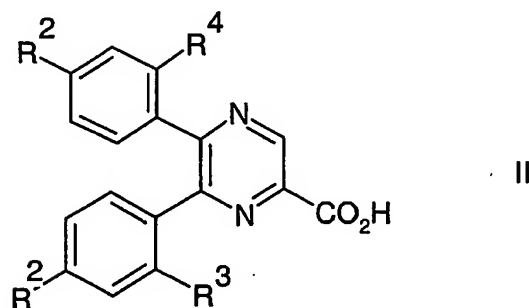
#### Methods of preparation

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The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the

compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula I may be prepared by reacting a compound of formula II



in which  $R^2$ ,  $R^3$  and  $R^4$  are as previously defined with an amine of formula III



in an inert solvent, for example dichloromethane, in the presence of a coupling agent, for example a carbodiimide, eg 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, and optionally in the presence of a catalyst, for example a basic catalyst, eg 4-dimethylamino-pyridine, at a temperature in the range of  $-25^\circ\text{C}$  to  $150^\circ\text{C}$ .

15 Compounds of formulae II and III may be prepared as described in the Examples and by other methods known to those skilled in the art.

Certain compounds of formula II in which  $R^2$ ,  $R^3$  and  $R^4$  are as previously defined are  
20 believed to be novel and are herein claimed as another aspect of the present invention with the exception of 5,6-diphenyl-2-pyrazinecarboxylic acid and 5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxylic acid.

The compounds of the invention may be isolated from their reaction mixtures using  
25 conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

#### Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient, or a pharmaceutically acceptable organic or inorganic addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

A compound of the invention may also be combined with other anti-obesity agents such as Orlistat or a monoamine reuptake inhibitor, for example Sibutramine. Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in

the treatment of disorders or conditions associated with obesity (such as type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatorrheic hepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

5

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

10

#### Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight which normally accompanies the cessation of smoking.

25

In another aspect the present invention provides a compound of formula I as claimed in any previous claim for use as a medicament.

30

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric

disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particularly suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.



ExamplesAbbreviations

DCM - dichloromethane

5 DMF - dimethylformamide

DMAP - 4-dimethylaminopyridine

EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

TEA - triethylamine

TFA - trifluoroacetic acid

10 DMSO - dimethyl sulfoxide

DEA - Diethylamine

PCC - Pyridinium chlorochromate

DCM - Dichloromethane

15 t triplet

s singlet

d doublet

q quartet

qvint quintet

20 m multiplet

br broad

bs broad singlet

dm doublet of multiplet

bt broad triplet

25 dd doublet of doublet

General Experimental Procedures

Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). <sup>1</sup>H NMR measurements were performed on either a  
30 Varian Mercury 300 or a Varian Inova 500, operating at <sup>1</sup>H frequencies of 300 and 500 MHz respectively. Chemical shifts are given in ppm with CDCl<sub>3</sub> as internal standard.

Purification was performed on a semipreparative HPLC with a mass triggered fraction collector, Shimadzu QP 8000 single quadrupole mass spectrometer equipped with 19 x 100 mm C8 column. The mobile phase used was, if nothing else is stated, acetonitrile and buffer (0.1 M NH<sub>4</sub>Ac:acetonitrile 95:5).

5

For isolation of isomers, a Kromasil CN E9344 (250 x 20 mm i.d.) column was used. Heptane:ethyl acetate:DEA 95:5:0.1 was used as mobile phase (1 ml/min). Fraction collection was guided using a UV-detector (330 nm).

## 10 Synthesis of intermediates

The following intermediates were not commercially available and therefore prepared as described in Preparation A, (Chem. Ber., 100, 1967, p. 555).

### Preparation A

15

#### (a) 5,6-diphenyl-pyrazine-2-carboxylic acid

The monohydrochloride of 2,3-diaminopropionic acid (500 mg, 3.56 mmol) and benzil (890 mg, 4.23 mmol) were added to a solution of sodium hydroxide (677 mg, 16.93 mmol) in methanol (10 ml). An extra portion of methanol was added (5 ml) and the reaction mixture was refluxed for 20 minutes. The mixture was cooled to 25°C and air was bubbled through for 30 minutes. Hydrochloric acid (aq, 2 M) was added until the reaction mixture reached pH 2. The solution was extracted with diethyl ether. The combined diethyl ether phases were dried (MgSO<sub>4</sub>), filtrated and evaporated under reduced pressure to give the crude product. MS *m/z* 277 (M+H)<sup>+</sup>. The crude product was used in steps described below without further purification.

25

#### (b) 5,6-Bis-(4-bromophenyl)-pyrazine-2-carboxylic acid

The title compound was prepared essentially as described in Preparation A step (a), using monohydrochloride of 2,3-diaminopropionic acid (600 mg, 4.26 mmol) and 4,4'-dibromobenzil (1.745 g, 4.26 mmol, 90 %) as starting materials. The reaction mixture was refluxed for 2 hours and air was bubbled through for 1 hour. Hydrochloric acid (aq, 2 M)

30

was added until pH 2. The mixture was evaporated under reduced pressure and the residue was dissolved in water. The solution was extracted with diethyl ether, the combined diethyl ether phases were dried ( $\text{MgSO}_4$ ), filtered and evaporated under reduced pressure. The crude product (500 mg, 27%) was used in steps described below without further purification. MS  $m/z$  435, 437, 439 ( $\text{M}+\text{H}$ )<sup>+</sup>.

(c) 5,6-Di-*p*-tolyl-pyrazine-2-carboxylic acid

The title compound was prepared as described in Preparation A step (a) using 4,4'-dimethylbenzil (848 mg, 3.56 mmol). The reaction mixture was however refluxed for 1 hour and air was bubbled through the reaction mixture for about 7 hours. The mixture was evaporated and the residue was dissolved in water. Hydrochloric acid (aq, 2 M) was added until pH 2 was reached. The solution was extracted with diethyl ether. The combined diethyl ether phases were dried ( $\text{MgSO}_4$ ), filtered and evaporated under reduced pressure. The crude product (918 mg, 85%) was used in steps described below without further purification. MS  $m/z$  305 ( $\text{M}+\text{H}$ )<sup>+</sup>.

(d) 5,6-Bis-(4-methoxyphenyl)pyrazine-2-carboxylic acid

The title compound was prepared as described in Preparation A step (c) using 4,4'-dimethoxybenzil (961 mg, 3.56 mmol) as starting material. The reaction mixture was refluxed over night and air was bubbled through the mixture for 8 hours. The crude product (435 mg, 36%) was used in steps described below without further purification. MS  $m/z$  335 ( $\text{M}+\text{H}$ )<sup>+</sup>.

(e) 5,6-Bis-(4-chlorophenyl) pyrazine-2-carboxylic acid

The title compound was prepared as described in Preparation A step (c) using 4,4'-dichlorobenzil (993 mg, 3.56 mmol). Reflux for 1 hour gave directly the crude product (923 mg, 75%) that was used in steps described below without further purification. MS  $m/z$  343, 345, 347 ( $\text{M}-\text{H}$ )<sup>-</sup>.

(f) 5,6-Bis-(2-chlorophenyl)pyrazine-2-carboxylic acid

The title compound was prepared as described in Preparation A step (c) using 2,2'-dichlorobenzil (993 mg, 3.56 mmol). The crude product (895 mg, 73%) was used in steps described below without further purification. MS  $m/z$  343, 345, 347 (M-H).

5 (g) 2-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)ethanone

A mixture of (4-Chlorophenyl)acetyl chloride (7.0 g, 73.0 mmol), 1,3-dichloro-benzene (42 ml, 370 mmol) and  $AlCl_3$  (6.9 g, 51.8 mmol) was stirred at 25 °C over night. Aqueous work-up and column chromatography ( $SiO_2$ , toluene:heptane 1:1) gave the title compound  
10 (2.70 g, 24%). MS  $m/z$  297, 299, 301 (M-H)

(h) 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)ethane-1,2-dione

2-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)ethanone (2.7 g, 9.01 mmol) was dissolved in 1,2-dichloroethane (25 ml) and freshly made PCC (3.89 g, 18.02 mmol), pyridine (1.43 g,  
15 18.02 mmol) and molecular sieves were added. The reaction mixture was refluxed under inert atmosphere overnight. The solution was cooled to 25 °C, filtered through Silica and then solvent was evaporated under reduced pressure. The crude product (1.9 g, 66%) was used directly in the next step.  $^1H$  NMR (500 MHz)  $\delta$  7.97 (d, 2H), 7.84 (d, 1H), 7.52 (d, 2H), 7.46 (s, 1H), 7.44 (d, 1H).

20 (i) 5-(4-Chlorophenyl)-6-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid and  
6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid

The title compounds were prepared as described in Preparation A step (a), using 1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)ethane-1,2-dione (1.85 g; 5.90 mmol) from  
25 Preparation A step (g) and the monochloride of 2,3-diaminopropionic acid (0.61 g, 5.90 mmol) as starting materials. The mixture was refluxed for 30 minutes and then directly worked-up. The crude product was allowed to stand over night to aromatise. Flash chromatography ( $SiO_2$ , DCM:methanol 10:1, 1% Acetic acid) gave the isomer mixture (0.2 g, 10%). MS  $m/z$  377, 379, 381 (M-H)

## Examples of the Invention

### Example 1

#### *N*-(1-piperidinyl)- 5,6-diphenyl-2-pyrazinecarboxamide

- 5 5,6-Diphenylpyrazine-2-carboxylic acid (500 mg, 1.81 mmol) from Preparation A, step (a), was dissolved in DCM (4 ml) and DMF (150  $\mu$ l). DMAP (22 mg, 0.18 mmol) and 1-aminopiperidine (218 mg, 2.17 mmol) were added and the solution was cooled to 0 °C. A slurry of EDC (1.99 mmol, in 2mL DCM and 100  $\mu$ l DMF) was added dropwise. The reaction mixture was stirred at 25 °C. After 17 hours additional 1-aminopiperidine (40 mg, 10 0.40 mmol) and EDC (76 mg, 0.40 mmol) was added, and the mixture was stirred for an additional 3 hours. The crude was diluted with DCM (5ml) and washed with a saturated solution of NaHCO<sub>3</sub>. The organic phase was dried (MgSO<sub>4</sub>), filtered and evaporated. Flash chromatography (SiO<sub>2</sub>, ethyl acetate:hexane 2:1) gave the subtitle compound (160 mg, 25%) as a white solid.
- 15 <sup>1</sup>H NMR (300 MHz)  $\delta$  9.41 (s, 1H), 8.52 (s, 1H), 7.50-7.29 (m, 10H), 2.94 (t, 4H), 1.81 (m, 4H), 1.50 (m, 2H).
- MS *m/z* 359 (M+H)<sup>+</sup>.

### Example 2

#### 20 *N*-(1-piperidinyl)- 5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide

- To 5,6-Bis-(4-bromophenyl)-pyrazine-2-carboxylic acid (108 mg, 0.25 mmol) from Preparation A, step (b), DMAP (0.025 mmol, in 500  $\mu$ l DCM), 1-aminopiperidine (0.25 mmol, in 1100  $\mu$ l DCM), EDC (0.27 mmol, in 1100  $\mu$ l DCM and cooled to 8 °C) were added. The reaction mixture was stirred at 25 °C for 20 h, then washed with saturated
- 25 NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>), filtered and evaporated. Semipreparatory HPLC (0.01% TEA in the buffered phase) gave the subtitle compound (6.7 mg, 5.4%).

$^1\text{H}$  NMR (300 MHz)  $\delta$  9.41 (s, 1H), 8.48 (s, 1H), 7.54 (d, 2H), 7.51 (d, 2H), 7.36 (d, 2H), 7.34 (d, 2H), 2.94 (t, 4H), 1.81 (m, 4H), 1.55-1.45 (m, 2H).

MS  $m/z$  515, 517, 519 (M+H) $^+$ .

5 Example 3

*N*-(1-piperidinyl)- 5,6-bis(4-methylphenyl)- 2-pyrazinecarboxamide

5,6-Di-*p*-tolyl-pyrazine-2-carboxylic acid (76 mg, 0.25 mmol) from Preparation A, step (c), was used as described in Example 2 to give the title compound (27 mg, 28%).

$^1\text{H}$  NMR (300 MHz)  $\delta$  9.35 (s, 1H), 8.57 (s, 1H), 7.38 (d, 4H), 7.18 (d, 2H), 7.13 (d, 2H),  
10 2.92 (t, 4H), 2.40 (s, 3H), 2.37 (s, 3H), 1.86-1.75 (m, 4H), 1.54-1.44 (m, 2H).

MS  $m/z$  387 (M+H) $^+$ .

Example 4

*N*-(1-piperidinyl)- 5,6-bis(4-methoxyphenyl)- 2-pyrazinecarboxamide

15 5,6-Bis-(4-methoxyphenyl)-pyrazine-2-carboxylic acid (84 mg, 0.25 mmol) from Preparation A, step (d), was used as described Example 2 to give the title compound (20 mg, 19%).

$^1\text{H}$  NMR (300 MHz)  $\delta$  9.31 (s, 1H), 8.57 (s, 1H), 7.46 (d, 2H), 7.44 (d, 2H), 6.90 (d, 2H), 6.86 (d, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.93 (t, 4H), 1.80 (m, 4H), 1.54-1.45 (m, 2H).

20 MS  $m/z$  419 (M+H) $^+$ .

Example 5

*N*-(1-piperidinyl)- 5,6-bis(4-chlorophenyl)- 2-pyrazinecarboxamide

25 5,6-Bis-(4-chlorophenyl)-pyrazine-2-carboxylic acid (86 mg, 0.25 mmol) from Preparation A, step (e), was used as described in Example 2 to give the subtitle compound (16 mg, 15%).

$^1\text{H}$  NMR (300 MHz)  $\delta$  9.40 (s, 1H), 8.49 (s, 1H), 7.45-7.31 (m, 8H), 2.94 (t, 4H), 1.80 (m, 4H), 1.54-1.45 (m, 2H).

MS  $m/z$  427, 429, 431 (M+H) $^+$ .

Example 6N-(1-piperidiny)- 5,6-bis(2-chlorophenyl)- 2-pyrazinecarboxamide

5,6-Bis-(2-chlorophenyl)-pyrazine-2-carboxylic acid (86 mg, 0.25 mmol) from Preparation A, step (f), was used as described in Example 2 to give the subtitle compound (6 mg, 6%).

5  $^1\text{H}$  NMR (300 MHz)  $\delta$  9.52 (s, 1H), 8.52 (s, 1H), 7.44-7.17 (d, 8H), 2.94-2.88 (t, 4H);  
1.85-1.70 (m, 4H), 1.52-1.44 (m, 2H).

MS  $m/z$  427, 429, 431 (M+H) $^+$ .

Example 7

10 N-cyclohexyl-5,6-diphenyl-2-pyrazinecarboxamide

5,6-diphenyl-pyrazine-2-carboxylic acid (70 mg, 0.25 mmol) from Preparation A, step (a), was reacted essentially as described in Example 2 but with cyclohexylamine (0.25 mmol, in 1 ml DCM), DMAP (0.025 mmol, in 0.5 ml DCM), EDC (0.28 mmol, in 1 ml DCM, and cooled to 8 °C) and DMF (100  $\mu$ l). Semipreparatory HPLC (0.15%

15 TFA/water:acetonitrile 95:5 instead of the buffer phase) gave the title compound (7 mg, 8%) after washing with  $\text{Na}_2\text{CO}_3$  solution.

$^1\text{H}$  NMR (300 MHz)  $\delta$  9.41 (s, 1H), 7.78 (d, 1H), 7.49-7.28 (m, 10H), 4.12-3.97 (m, 1H), 2.13-1.23 (m, 10H).

MS  $m/z$  358 (M+H) $^+$ .

20

Example 8N-cyclohexyl-5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-bromophenyl)-pyrazine-2-carboxylic acid (109 mg, 0.25 mmol) from Preparation A, step (b), was used as described in Example 7. Semipreparatory HPLC (0.15%  
25 TFA/water:acetonitrile 95:5 instead of the buffer phase) gave the title compound (7 mg, 8%) after washing with  $\text{Na}_2\text{CO}_3$  solution.

$^1\text{H}$  NMR (300 MHz)  $\delta$  9.41 (s, 1H), 7.68 (s, 1H), 7.54 (d, 2H), 7.50 (d, 2H), 7.36 (d, 2H), 7.34 (d, 2H), 4.11-3.96(m, 1H), 2.12-1.20 (m, 10H).

MS  $m/z$  514, 516, 518 (M+H) $^+$ .

30

Example 9N-cyclohexyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide

5,6-Di-*p*-tolyl-pyrazine-2-carboxylic acid (76 mg, 0.25 mmol) from Preparation A, step (c), was used as described in Example 7. Semipreparatory HPLC (0.01% TEA in the buffer phase) gave the subtitle compound (4 mg, 4%).

<sup>1</sup>H NMR (300 MHz) δ 9.36 (s, 1H), 7.77 (d, 1H), 7.39 (d, 4H), 7.18 (d, 2H), 7.13 (d, 2H), 4.10-3.96 (m, 1H), 2.40 (s, 3H), 2.37 (s, 3H), 2.09-1.20 (m, 10H).

MS *m/z* 386 (M+H)<sup>+</sup>.

10 Example 10N-cyclohexyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-methoxyphenyl)-pyrazine-2-carboxylic acid (76 mg, 0.25 mmol) from Preparation A, step (d), was used essentially as described in Example 7 but the reaction mixture was first stirred overnight, then more cyclohexylamine (25 mg, 0.25 mmol) was added and the mixture was stirred for an additional two days prior to workup.

15 Semipreparatory HPLC (0.15 % TFA in the buffered phase) gave the title compound (12 mg, 11%).

<sup>1</sup>H NMR (300 MHz) δ 9.32 (s, 1H), 7.76 (d, 1H), 7.47 (d, 2H), 7.45 (d, 2H), 6.90 (d, 2H), 6.86 (d, 2H), 4.10-3.96 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 2.09-1.17 (m, 10H).

20 MS *m/z* 418 (M+H)<sup>+</sup>.

Example 11N-cyclohexyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-chlorophenyl)pyrazine-2-carboxylic acid (86 mg, 0.25 mmol) from Preparation A, step (e), was used as described in Example 10 to give the title compound (7 mg, 8%) after washing with Na<sub>2</sub>CO<sub>3</sub> solution.

<sup>1</sup>H NMR (300 MHz) δ 9.41 (s, 1H), 7.69 (s, 1H), 7.47-7.30 (m, 8H), 4.10-3.97 (m, 1H), 2.10-1.18 (m, 10H).

MS *m/z* 426, 428, 430 (M+H)<sup>+</sup>.



Example 12N-cyclohexyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide

5,6-Bis-(2-chlorophenyl)-pyrazine-2-carboxylic acid (86 mg, 0.25 mmol) from preparation

A step (f) was used as described in Example 10, to give the title compound (14 mg, 13%).

5  $^1\text{H}$  NMR (300 MHz)  $\delta$  9.51 (s, 1H), 7.74 (s, 1H), 7.41-7.18 (m, 8H), 4.10-3.97 (m, 1H),  
2.07-1.14 (m, 10H).

MS  $m/z$  426, 428, 430 (M+H) $^+$ .

Example 1310 N,5,6-triphenyl-2-pyrazinecarboxamide

To 5,6-Diphenyl-pyrazine-2-carboxylic acid (70 mg, 0.25 mmol) from Preparation A, step (a), DMAP (0.025 mmol, in 0.5 ml DCM), aniline (0.25 mmol, in 1 ml DCM), EDC (0.28 mmol, in 1ml DCM, cooled to 8 °C) and DMF (100  $\mu$ l) were added. The reaction mixture was stirred at 25 °C over night, then worked up as described in Example 2.

15 Semipreparatory HPLC (0.15 % TFA/water:acetonitrile 95:5 instead of the buffer phase) gave the title compound (27 mg, 30%) after washing with Na<sub>2</sub>CO<sub>3</sub> solution.

$^1\text{H}$  NMR (300 MHz)  $\delta$  9.75 (s, 1H), 9.52 (d, 1H), 7.80 (d, 2H), 7.55-7.32 (m, 12H), 7.20 (t, 1H).

MS  $m/z$  352 (M+H) $^+$ .

20

Example 14N-phenyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide

5,6-Di-*p*-tolyl-pyrazine-2-carboxylic acid (77 mg, 0.25 mmol) from Preparation A, step (c), was used as described in Example 13 to give the subtitle compound (28 mg, 29%).

25  $^1\text{H}$  NMR (500 MHz)  $\delta$  9.78 (s, 1H), 9.49 (s, 1H), 7.81 (d, 2H), 7.47-7.43 (m, 6H), 7.25-7.17 (m, 5H), 2.45 (s, 3H), 2.41 (s, 3H).

MS  $m/z$  380 (M+H) $^+$ .

Example 15N-phenyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-methoxyphenyl)-pyrazine-2-carboxylic acid (85 mg, 0.25 mmol) from Preparation A step (d), was used as described in Example 13, to give the title compound  
5 (33 mg, 32%).

$^1\text{H}$  NMR (300 MHz)  $\delta$  9.74 (s, 1H), 9.42 (s, 1H), 7.79 (d, 2H), 7.50 (d, 4H), 7.42 (t, 2H), 7.19 (t, 1H), 6.94 (d, 2H), 6.89 (d, 2H), 3.88 (s, 3H), 3.85 (s, 3H).

MS  $m/z$  412 (M+H) $^+$ .

10 Example 16N-phenyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide

5,6-Bis-(4-chlorophenyl)-pyrazine-2-carboxylic acid (87 mg, 0.25 mmol) from Preparation A, step (e), was used as described in Example 13, to give the subtitle compound (6 mg, 6%).

15  $^1\text{H}$  NMR (300 MHz)  $\delta$  9.66 (s, 1H), 9.52 (s, 1H), 7.79 (d, 2H), 7.48-7.35 (m, 10H), 7.21 (t, 1H).

MS  $m/z$  420, 422, 424 (M+H) $^+$ .

Example 1720 N-phenyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide

5,6-Bis-(2-chloro-phenyl)-pyrazine-2-carboxylic acid (87 mg, 0.25 mmol) from Preparation A, step (f), was treated as described in Example 13, to give the title compound (27 mg, 25%).

$^1\text{H}$  NMR (500 MHz)  $\delta$  9.73 (s, 1H), 9.66 (s, 1H), 7.81(d, 2H), 7.46-7.22 (m, 11H).

25 MS  $m/z$  420, 422, 424 (M+H) $^+$ .

Example 18

5-(4-Chlorophenyl)-6-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid piperidin-1-ylamide and 6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid piperidin-1-ylamide.

5

The mixture of 5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid and 6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)pyrazine-2-carboxylic acid (78 mg, 0.205 mmol) from Preparation A step (i) and thionyl chloride (147 mg, 1.23 mmol) were refluxed in toluene (2ml) for 3 hours. The solvent and reagents were evaporated under reduced  
10 pressure and the intermediates were dissolved in DCM (1 ml). TEA (42 mg, 0.41 mmol) and 1-aminopiperidine (21 mg, 0.205 mmol) were dissolved in DCM (1ml) and added. The reaction mixture was stirred at 25 °C overnight and then evaporated under reduced pressure. Flash chromatography (SiO<sub>2</sub>, heptane:ethyl acetate 1:1) gave a mixture of the title compounds (45 mg, 47%, ratio of isomers 0.5:1). <sup>1</sup>H NMR (300 MHz) δ 9.46 (s, 1H), 8.39  
15 (s, 1H), 7.47-7.28 (m, 7H), 3.02-2.84 (m, 4H), 1.89-1.73 (m, 4H), 1.57-1.41 (m, 2H) and 9.42 (s, 1H), 8.51 (s, 1H), 7.47-7.28 (m, 7H), 3.02-2.84 (m, 4H), 1.89-1.73 (m, 4H), 1.57-1.41 (m, 2H).

Example 18 (a)

20 N-(1-piperidinyl)- 5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)-2-pyrazinecarboxamide

The titled compound was isolated from the mixture prepared in Example 18 (35 mg) by preparative chromatography (9 mg, 26%). <sup>1</sup>H NMR (300 MHz) δ 9.46 (s, 1H), 8.38 (s, 1H), 7.46-7.24 (m, 7H), 2.89 (t, 4H), 1.78 (p, 4H), 1.52-1.40 (m, 2H).

25 Example 18 (b)

N-(1-piperidinyl)- 6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-pyrazinecarboxamide

The titled compound was isolated from the mixture prepared in Example 18 (35 mg) by preparative chromatography (11 mg, 31%). <sup>1</sup>H NMR (300 MHz) δ 9.42 (s, 1H), 8.50 (s, 1H), 7.39-7.30 (m, 7H), 2.93 (t, 4H), 1.80 (p, 4H), 1.54-1.43 (m, 2H).

30

### Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al, Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

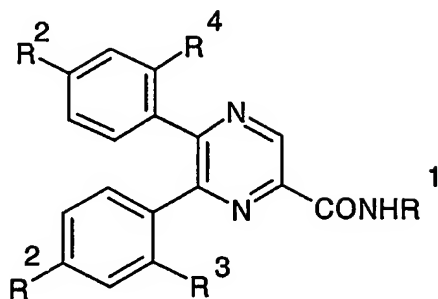
10  $10\mu\text{g}$  of membranes prepared from cells stably transfected with the CB1 gene were suspended in  $200\mu\text{l}$  of  $100\text{mM}$  NaCl,  $5\text{mM}$   $\text{MgCl}_2$ ,  $1\text{mM}$  EDTA,  $50\text{mM}$  HEPES (pH 7.4),  $1\text{mM}$  DTT,  $0.1\%$  BSA and  $100\mu\text{M}$  GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and  $0.1\mu\text{Ci}$  [ $^{35}\text{S}$ ]-GTP $\gamma\text{S}$ . The reaction was allowed to proceed at  $30^\circ\text{C}$  for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer ( $50\text{mM}$  Tris (pH 7.4),  $5\text{mM}$   $\text{MgCl}_2$ ,  $50\text{mM}$  NaCl). Filters were then covered with scintillant and counted for the amount of [ $^{35}\text{S}$ ]-GTP $\gamma\text{S}$  retained by the filter.

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation  $y=A+((B-A)/(1+((C/x)^D)))$  and the IC50 value determined as the concentration required to give half maximal inhibition of GTP $\gamma\text{S}$  binding under the conditions used.

The compounds of the present invention are active at the CB1 receptor ( $\text{IC}_{50} < 1$  micromolar). Most preferred compounds have  $\text{IC}_{50} < 200$  nanomolar.

Claims

1. A compound of formula I



and pharmaceutically acceptable salts, solvates and crystalline forms thereof, in which

R¹ represents cyclohexyl, 1-piperidinyl or phenyl ;

R² represents H, chloro, bromo, methyl or methoxy; and

when R³ represents H, R⁴ represents H or chloro; and

when R³ represents chloro, R⁴ represents H or chloro.

2. A compound according to claim 1 in which R¹ represents cyclohexyl.

3. A compound according to claim 1 in which R¹ represents 1-piperidinyl.

4. A compound according to claim 1 in which R¹ represents phenyl.

5. A compound selected from:

*N*-(1-piperidinyl)- 5,6-diphenyl-2-pyrazinecarboxamide;

*N*-(1-piperidinyl)- 5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide;

*N*-(1-piperidinyl)- 5,6-bis(4-methylphenyl)- 2-pyrazinecarboxamide;

*N*-(1-piperidinyl)- 5,6-bis(4-methoxyphenyl)- 2-pyrazinecarboxamide;

*N*-(1-piperidinyl)- 5,6-bis(4-chlorophenyl)- 2-pyrazinecarboxamide;

*N*-(1-piperidinyl)- 5,6-bis(2-chlorophenyl)- 2-pyrazinecarboxamide;

*N*-cyclohexyl-5,6-diphenyl-2-pyrazinecarboxamide;

*N*-cyclohexyl-5,6-bis(4-bromophenyl)-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide;  
*N*-cyclohexyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide;  
5 *N*-cyclohexyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide;  
*N*,5,6-triphenyl-2-pyrazinecarboxamide;  
*N*-phenyl-5,6-bis(4-methylphenyl)-2-pyrazinecarboxamide;  
*N*-phenyl-5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxamide;  
*N*-phenyl-5,6-bis(4-chlorophenyl)-2-pyrazinecarboxamide;  
10 *N*-phenyl-5,6-bis(2-chlorophenyl)-2-pyrazinecarboxamide;  
*N*-(1-piperidinyl)-5-(4-chlorophenyl)-6-(2,4-dichlorophenyl)-2-pyrazinecarboxamide; and  
*N*-(1-piperidinyl)-6-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-2-pyrazinecarboxamide;  
and where applicable, optical isomers, tautomers, stereoisomers and racemates thereof as  
well as pharmaceutically acceptable salts, solvates and crystalline forms thereof.

15

6. A compound of formula I as claimed in any previous claim for use as a medicament.

7. A pharmaceutical formulation comprising a compound of formula I, as defined in any one of claims 1 to 5 and a pharmaceutically acceptable adjuvant, diluent or carrier.

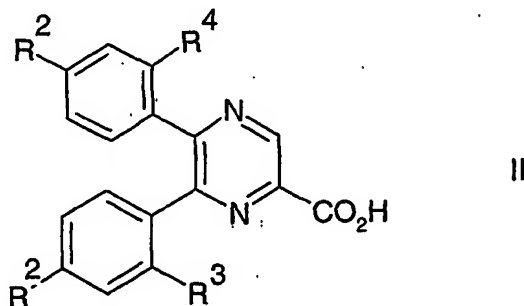
20

8. Use of a compound of formula I, as defined in any one of claims 1 to 5 in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxiety-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related  
25 conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse  
30 indications.

9. A method of treating obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as  
 5 dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 5 to a patient in need  
 10 thereof.

10. A compound as defined in any one of claims 1 to 5 for use in the treatment of obesity.

11. A process for the preparation of a compound of formula I comprising reacting a  
 15 compound of formula II



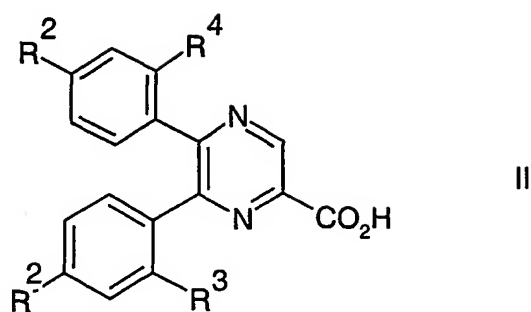
in which  $R^2$ ,  $R^3$  and  $R^4$  are as previously defined with an amine of formula III

20



in an inert solvent in the presence of a coupling agent, and optionally in the presence of a catalyst, at a temperature in the range of  $-25^\circ\text{C}$  to  $150^\circ\text{C}$ .

12. A compound of formula II



in which

$R^1$  represents cyclohexyl, 1-piperidinyl or phenyl ;

5  $R^2$  represents H, chloro, bromo, methyl or methoxy; and

when  $R^3$  represents H,  $R^4$  represents H or chloro; and

when  $R^3$  represents chloro,  $R^4$  represents H or chloro,

with the exception of 5,6-diphenyl-2-pyrazinecarboxylic acid and 5,6-bis(4-methoxyphenyl)-2-pyrazinecarboxylic acid.



## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 02/05736

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D241/24 A61K31/4965 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| X          | EP 0 397 859 A (TERUMO CORP.)<br>22 November 1990 (1990-11-22)<br>claims; example 14; table 1                                   | 12                    |
| A          | claims  | 1,3,6-11              |
| A          | WO 92 02513 A (FUJISAWA)<br>20 February 1992 (1992-02-20)<br>cited in the application<br>page 1 -page 5; claims; examples 26,27 | 1-12                  |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*G\* document member of the same patent family

Date of the actual completion of the international search

1 April 2003

Date of mailing of the international search report

23/04/2003

Name and mailing address of the ISA

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Authorized officer

Francois, J

# INTERNATIONAL SEARCH REPORT

national application No.  
PCT/GB 02/05736

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 02/05736

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
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